**Review Article** **Neurobiology**

**International Journal of Pharma and Bio Sciences**

**ISSN 0975-6299**

# ALZHEIMER'S AND PERSPECTIVES FROM MEDICINAL PLANTS AS THERAPEUTICS: A REVIEW

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## ABSTRACT

Alzheimer's disease is a brain disorder characterized by a progressive dementia that occurs in usually middle or late life period of an individual. There are upsurging evidences that oxidative stress is mostly responsible to the dementia. There are many drugs in the market recommended for dementia, which shows affect on diseased patients only up to minimal level, but after sometimes their suffering continues. Many drugs like Bryostatin 1, Crenezumab are there which shows promising results in clinical trials, but many shows failure after going through trials, few of them are Avagacestat, Ponezumab, etc. They also shows side effects like, indigestion, nausea, weight loss, loss of appetite and loss of strength which makes the case even worse. To rectify these activities of drugs or to avoid these, administration of secondary metabolites perhaps shows some satisfying results. Many ongoing researches on plant's secondary metabolites like curcumin, tocopherol which are already been commercialized, shows ability to cure amyloid and tau related problems which causes dementia. Regular consumption of these nutritive substances may prevent the effects of oxidative effect on cells which causes AD.

**KEYWORDS**: **Alzheimer's disease, Presenile, Secondary metabolites, Dementia, Oxidative stress , Amyloid**

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**Received on : 06-09-2016**
**Revised and Accepted on : 17-11-2016**
**DOI: http://dx.doi.org/10.22376/ijpbs.2017.8.1.b202-214**

## INTRODUCTION

Alzheimer's disease is a neurodegenerative disease which is related to age in progressive manner, impeding memory and other brain operations[1]. The disease invades individual's memories, relationships and their persona, ability to care themselves and finally their life. In accordance to Alzheimer's Associations, Alzheimer's disease holds 6$^{th}$rank in U.S.A having 5.4 million people suffering and counting. It is expecting that, the number of affected people will reach up to 106.8 million by 2050 worldwide[2]. Characteristics of Alzheimer's disease show advancement of arrears in more than one area of cognition, episodic memory, language, praxis and attention[3-4] Literature survey also reveal other symptoms regarding this disease like, impaired memory, distortion in functioning of cognition, alteration in behavior, in appropriation in social behavior, declination in functioning in language[5]. Clinical diagnosis of AD is depends on it's barring criteria which is only possible through necropsy[6]. It also based on patient's previous records and clinical assessment and neuropsychological appraisals[7-8]. In the context of diagnosis, the Positron Emission Tomography combined with various radiochemical endorsed to conjure up both amyloid plaques and neurofibrillary tangles, apart from this single photon emission computed tomography (SPECT) proves more advantageous in segregating the disorder from normal conditioned brain.Molecules in the serum or cerebrospinal fluid of diseased individual has been identified by using different parameters which helps in identifying the potential of the disease[7].For the pathogenesis of AD both environmental and genetic factors equally contribute[1]. More than a decade, it was already proposed that neurodegeneration in Alzheimer's disease is may be due to deposition of amyloid beta peptide (Aβ) in plaques in brain tissues[9]. Many literatures also proposed about some other causes which are responsible for AD, are mitochondrial dysfunction and oxidative stress[10-11].It is very interesting to know about amyloid beta theory and it is over production which brings on the evolution of secretase inhibitor, active and passive immunization approach. In spite of that, the drugs which are currently present in the market, like donepezil, memantine, revastagmine etc., are restricted in some extent[12]. Apart from synthetic medicines, herbal medicines in many cases proves to be more effective, due to its cultural eminence, consonance with human body, negligible side effects, due to all these reasons herbal medicines are upholder of many developing countries containing about 75-80% of population[3]. Many literature surveys approve that administration of herbal medicines shows improvement in learning memory in diseased patients[13-15].

## CAUSATIVE AGENTS OF AD

Intensive cognitive studies has been carried out globally in different rating scales of patient's group, in this irresistible consequences of neuro degeneration has been observed, these are bizarre thinking and behavior[16-19]. Several literature shows that AD could also be caused by different reasons shown in table 1 like, mutation in the gene coding for amyloid peptide protein, excision of amyloid beta from haploprotein by β-APP cleaving enzyme (BACE)[20-26].

**Table 1**
***Showing in the findings of causes of AD since 1994-2014***

| Year | Causes | References |
|---|---|---|
| 1994 | Synapse loss occur at an early stage of protein amyloid fibril deposition[10] | (10) |
| 1998 | tau phosphorylation and helical filaments assembly, due to inability of binding of ApoE4 to tau protein[6] | (6) |
| 1999 | Transfection of Asp2 into APP expressing cells results in an increase in the β- secretase activity[20] | (20) |
| 2000 | Hypothesis of 13 different aspects responsible for AD[27] | (27) |
| 2001 | Mutation in amyloid precursor protein increases protofibril formation and decrease in A β plasma level[28] | (28) |
| 2002 | Soluble oligomers of A β may be responsible for synaptic dysfunction in AD brains[28] | (28) |
| 2003-2004 | ApoE fragments generated in neurons in AD brains and can interact with tau and phosphorylated neurofilamants of high molecular weight resulting in large filamentous intracellular inclusions in neuronal cells[29,59] | (29, 58) |
| 2005 | Post translation modification of tau protein[30] | (30) |
| 2006 | Loss of Atg 7 (autophagy related 7), a gene essential for autophagy results limb clasping reflexes[26] | (26) |
| 2007 | Identified disease susceptible genes (e.g. ACE1, CHRNB2)[31] | (31) |
| 2008 | Oxidative stress[32] | (32) |
| 2009 | Decrease in cerebral blood flow[33] | (33) |
| 2011 | Hypothesis of autosomal mutation in presenillin1 (PSEN1 & PSEN2)[4] | (4) |
| 2012 | Autosomal dominant inheritance of genes amyloid precursor protein (APP) and presenillin (PSEN) genes[34] | (34) |
| 2013 | P73 haplosufficiency epitomize risk factor for tau hyperphosphoryration[35] | (35) |

## GLUTAMATE TRANSPORTER SYSTEM: POSSIBLE CAUSE OF AD

Glutamate excitory actions are negotiate by three types of receptors for NMDA (N-methyl-D-aspartate), kainite and quisqualate. The main astroglial glutamate transporter i.e. GLT-1 is oxidatively modified by 4-hydroxyl nonenal (HNE) when they are bind together. This is a lipid peroxidation product formed on the inferior parietal region of the brain of the individual suffering from neurodegenerative[36]. Abnormality in GLT-1 glutamate transporter system and momentous decrement of this system in cortex has been reported in diseased brain[4]. Addition of Aβ peptides in synaptosomes leads to lipid peroxidation[36-38]and increase the chances of binding of HNE to GLT-1[36], increases the amount of Aβ (1-42) which has affinity to bind with HNE, binds to GLT-1. In AD, when functioning of glutamate transport restricted, extraneuronal glutamate increases with subsequent inactivation of NMDA receptors and excitotoxic reactions involves accumulation of calcium results cell death with malfunctioning of tau protein expression shown in fig. I and II[39].

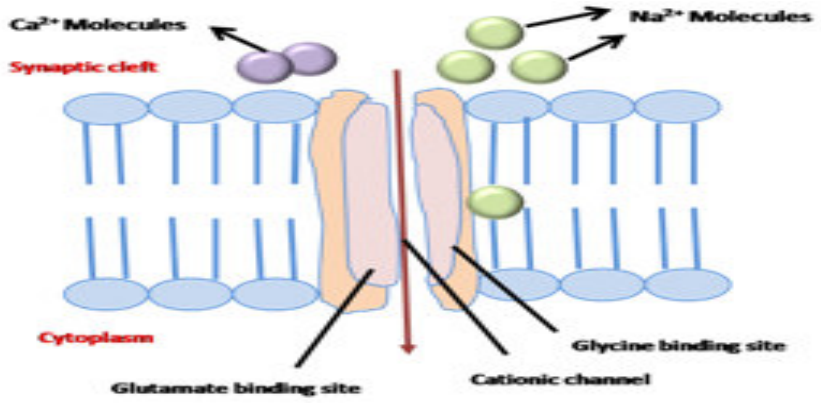


**Figure I**

***Showing transportation of calcium ions ($Ca^{2+}$) and sodium ions ($Na^{2+}$) in cell and glutamate binding site[39].***

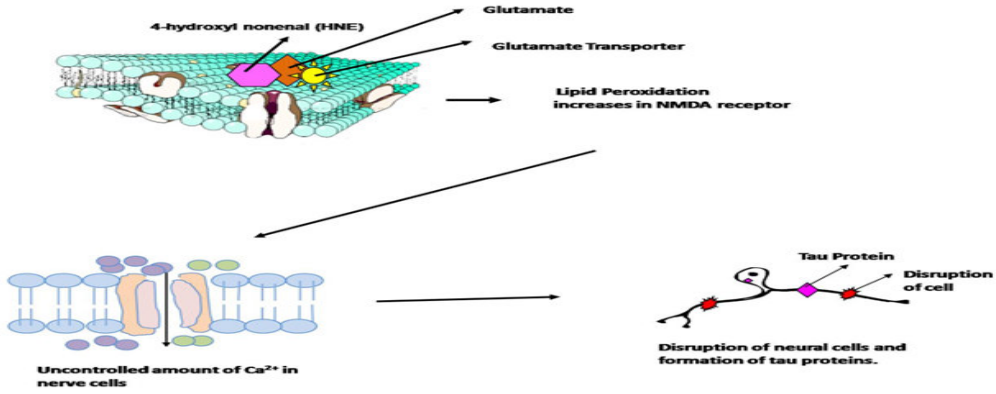


**Figure II**

***Showing normally, glutamate attached to glutamate transporter, then it carried by N-methyl-aspartate receptor to nerve cells where it release control amount of calcium ions for functioning of nerve cells to carry message. but in diseased case, when glutamate attached to glutamate transporter, modified 4-hydroxyl nonenal got attached to glutamate transporter results to lipid peroxidation which increase the stimulation of N-methyl-aspartate receptor which release the uncontrolled amount of calcium ions which results in disruption of nerve cells formation of deformed tau protein results in amyloid beta plaque formation[39].***

## TAU PROTEIN MALFUNCTION

Distinctive feature of AD is accumulation of neurofibrillary tangles (NFTs) in the brain.The composition of NFTs involves paired helical filaments (PHFs) and straight (SFs) dissimilar to any normal neural fibrils.Tau protein is one of the major protein components of paired helical filament[40-41]. Tau is typically a cytosolic protein, to which obligate the stabilization of microtubule assembly from tubulin subunit. Biochemical dysfunction of tau in PHFs is due to abnormal hyperphosphorylation and other post translation modification, like glycosylation, ubiquitation, polyamination, nitration, proteolysis, in addition to being aggregated. Many literatures have demonstrated these perilous post transition of normal tau to toxic molecule which aggregate into PHFs/SFs and causes neurofibrillary degeneration in AD shown in fig. 3. The main cause for hereditary frontal temporal dementia is due to devising of tau mutation[30,42-44].

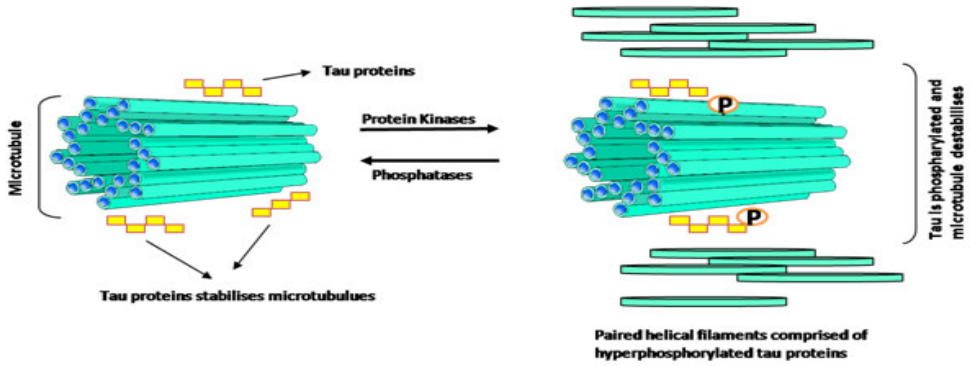


**Figure III**

***Tau protein stabilizes microtubule, when it gets phosphorylated, results in destabilization of microtubule. Lastly, tau protein does not able to stabilize microtubule assembly from tubulin subunits results degeneration of neurofibres[30,42-44].***

## GENE MUTATION

Mutation may be the reason for AD; they could be APP, PS1 or PS2 which increases Aβ deposition, but still they shows no simple interdependence with age at which it first shows symptoms[6,45]. As a matter of fact, some presenillis in mutation escalate the Aβ metabolism which symptoms such as weakness which affects the lower periphery[22, 46-48] and the manifestation of "cotton wool" plaques, with early AD onset. However, the symptoms which distinguishes itself in due course, but not the bygone, is may be due elevation of apoE4 alleles[49]. They may associate to the point that the cell culture does not show any sufficient reflection about the complexity of Aβ prudence in brain, as the reason for phenotypic variations are not clear.

## PREVALENCE

Millions of people worldwide have AD and other dementias shown in table 2. In 2013, around 44.4 million of people are suffering with dementia. This number will increment upto 75.6 million in 2030 and about 135.5 million in 2050. About 62% of individuals differing from dementia residing in developing countries, nevertheless by 2050 this will raise upto 71% shown in figure IV. Every year about 7.7 million new cases of dementia comes up, insinuating that there will be new case of dementia in every 4 seconds[50].

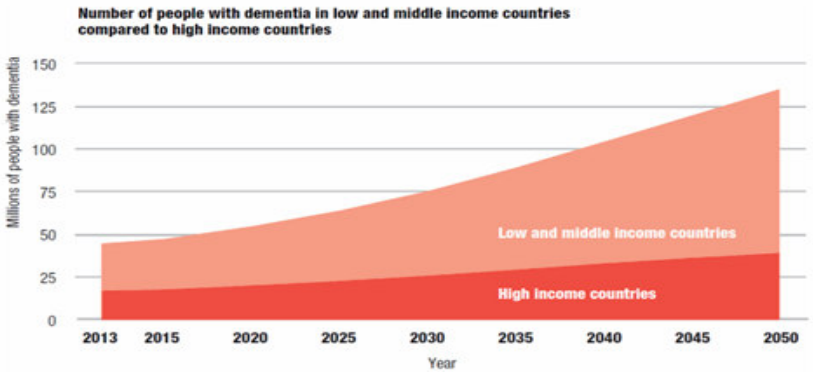


**Figure IV**

***Showing number of individuals with dementia in middle and low economy countries compared to high economy countries***

***The numbers showing prevalent cases describe the magnitude of the burden of AD on the community and the health –care system, but it does not provide an estimate 5 million people aged 65 years and older and approximately 200,000individuals younger than 65 years who have younger onset of AD[7] (7).***

## DEVELOPMENT OF THERAPEUTICS FOR AD

The identification of major path physiological mechanism in for AD has led the discovery of molecular earmark for the development of specific drugs. Till date, there are about 200 pharmaceutical compounds and counting is present day undergoing 2 and 3 trials[51]. These pharmaceutical compound are divided into according to targets, like, anti-amyloid drugs and targeting other pathological pathways[23]. The resultant effect of extracellular Aβ oligomers and fibrillary forms synaptic dysfunction, affect exons and dendritic spines, leads to neuronal loss[52].Thus, pharmacological compounds that show promising altitude towards Aβ clearance or prevention against aggregation epitomize the strategy to delay the advancement of the pathological processes of disease[53]. From literatures, association of AD can be seen with loss of cholinergic

neurons in the basal forebrain. Cholinergic neurons have uniqueness in its metabolism that shows their contribution in their vulnerability in AD and aging. The neurons use choline for major two objectives: - a) phosphorylates into phosphocholine, further transformed into membrane phosphotidyl choline; b) acetylated into transmitter acetylcholine[40]. Wurtman has found that aging and AD shows association with decrement of choline uptake in synthesizing neurons. These results bring changes in membrane composition which supplementsthe conversion which supplements the conversion of APP to damaged amyloid[54].

**Table 2**
***Showing compounds targeted to different causes for AD.***

| Compound | Company/institution | Target | Treatment | Current Phase | References |
|---|---|---|---|---|---|
| Bapineuzumab | Elan/Wyeth | Amyloid β deposition | Vaccine | Phase I ongoing[18] | (18) |
| Bryostatin 1 | Blanchette Rockefeller Neurosciences Institute | Decreases Amyloid β | Monoclonal antibody | Clinical trial Phase II[23] | (23) |
| EHT-0202 | ExonHit | GABA | α-secretaseactivator | Phase II clinical trial[18] | (18) |
| Solanezumab | Eli Lily | Amyloid β | monoclonal antibody | Phase III[23] | (23) |
| Ponezumab | Pfizer Inc. | Amyloid β | Monoclonal antibody | Interrupted at phase II[28] | (28) |
| Ganterezumab | Washington University School of Medicine | Amyloid β | Monoclonal antibody | Phase I[7] | (7) |
| Crenezumab | Roche | Amyloid β | Monoclonal antibody | Phase II[58] | (58) |
| Avagacestat | Bristol Meyers Squibb | gamma-secretase | Inhibitor | Interrupted at Phase II[7] | (7) |
| GRL-843[29] | Oklahoma Foundation Medical Research | BACE1 | Inhibitor | Ongoing[55] | (55) |
| TAK-070[30] | Takda Pharmaceutical Company Limited | BACE1 | Inhibitor | Clinical trial[58] | (58) |
| CHF5074 | Chiesipharmaceutical | Inflammation | Nonsteroidantinflammatory agent | Clinical trial phase III[58] | (58) |
| Curcumin | Linkoeping University | Amyloid Beta | Aggregator | Ongoing[56] | (56) |
| PBT-2 | Prana Biotechnology Ltd | Amyloid Beta | Inhibitor | Phase III[55] | (55) |
| Scyllo-cyclohexanehexol | Transition Therapeutics | Amyloid Beta | Inhibitor | Phase II clinical trials[55] | (Yan et al., 1999) |
| AVP923 | Alzheimer's disease education and referral centre | NMDA receptor Antagonist | Inhibitor | Phase II clinical trial[55] | (55) |
| Donepezil | Eisai Company Inc. and Pfizer | AchE | Inhibitor | Approved for all stages[50] | (50) |
| Galantamine | Janssen Pharmaceticals | AchE | Inhibitor | Approved for Mild to moderate[50] | (50) |
| Memantine | H. Lundback | N-metyl-D-aspartate receptor | Inhibitor | Approved for Moderate to severe[50] | (50) |
| Rivastigmine | Actavis Inc. | AchE | Inhibitor | Approved for Mild to moderate[50] | (50) |
| Tacrine | Parke Davis of Morris Plain, New Jersey, Warner Labert Company. | AchE | Inhibitor | Mild to moderate[50] | (50) |

***When there was no cure of AD, US Food & Administration (FAD) approved five drugs to treat its symptoms. Tacrine is the first cholinesterase inhibitors was approved in 1993 shown in table 3.***

## ANTI-ACETYLCHOLINESTERASE

Anti-acetylcholinesterase are group of drugs which are prescribes to cure symptoms related to memory, language, thinking, judgment and other thought relates functions.

## MODE OF ACTION OF ACETYLCHOLINESTERASE

In diseased condition, cells that produce and use acetylcholine, got damaged which reduces the amount of carrying messages shown in figure V and VI.The disintegration of acetylcholine by hindered the activity of acetylcholinesterase. For compensation of loss of functioning brain cells, these drugs help to maintain the acetylcholine levels. For example: galantamine one of the anti AChE drugs which revitalize the release of acetylcholine and build up many messages receiving nerve cells. Blockage of activation of another enzyme which is responsible for breakdown of acetylcholine is done by rivastigimine[50].

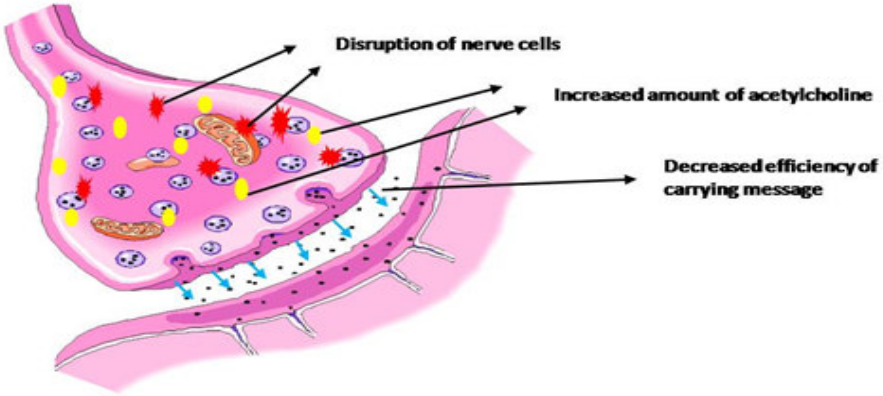


**Figure V**
***Showing, in diseased case, nerve cells got disrupted due to which increased amount of acetylcholine is produced which reduces the amount available to carry message through nerve cells[50]***

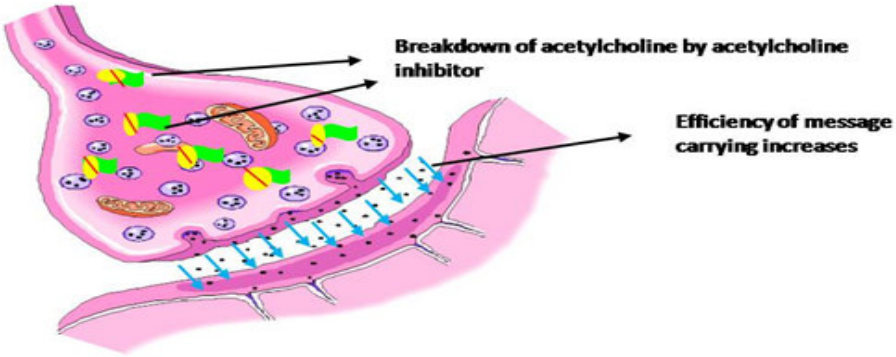


**Figure VI**
***Showing, when acetylcholine inhibitor administered there will be breakdown of acetylcholine and hence there will no damage in nerve cells[50]***

## N-METYL-D-ASPARTATE RECEPTOR ANTAGONIST TYPE DRUG

Memantine is one of the first discovered by drug for NMDA antagonist who is recommended for improving memory, attention, reason, language and capability to carry out, simple tasks. From moderate to severe stage, memantine has ability to treat AD, but memantine was refused by FDA for approval for treatment of mild Alzheimer's.

## MODE OF ACTION OF N-METYL-D-ASPARTATE RECEPTOR ANTAGONIST TYPE DRUG

NMDA drugs mainly control the regulation of activity of glutamate.The calcium ameliorates to create, chemical domain which is required for storing of information. These amounts of calcium are controlled in nerve by glutamate which participates in learning and memory by activating NMDA receptor. In diseased case, overstimulation of NMDA receptors allow enormous amount of calcium into nerve cells, that results to cessation of cells. To prevent this condition of cells, memantine partially blocks the NMDA receptors shown in figure VII(7).Scientists are still unable to understand the correct pathophysiology and mechanism of disease and its progression. Thus the selection of viable and effective targets for new medicines becomes very difficult. The development of *in vivo* models for AD is still a barrier in preclinical testing limiting the development of new entities.The unavailability of non-invasive biomarker delays the diagnosis of disease and its progression, makes detectability challenging in patients. This leads to long and expensive clinical trials[50].

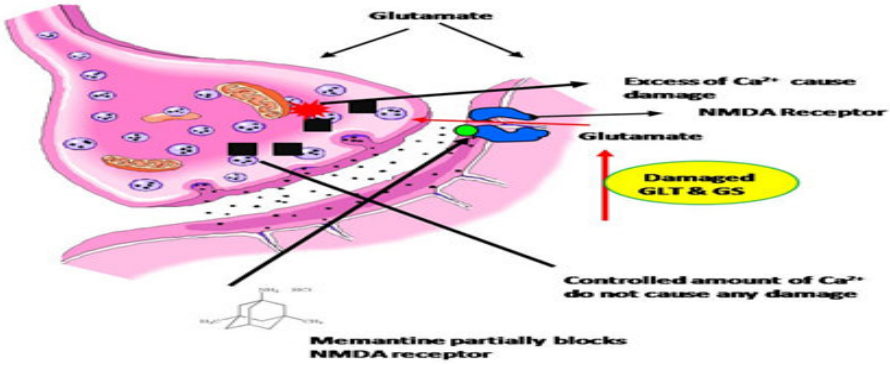


**Figure VII**

***Showing, action of memantine against cell disruption which later form AD. In this we can see glutamate which is already present in nerve cells, transported through glutamate transport system (GLT & GS), control the transport of calcium in nerve cell, if the transporter system got damaged then NMDA receptor will not able to control the amount of calcium in nerve cells which cause insertion of excessive amount of calcium in cells results to disruption. When memantine administered, it protect the cells by antagonizing surfeit amount of molecules of glutamate, produces by preventing it in some extent in the NMDA receptor, hence cell will not disrupt[50].***

**Table 3**

***Showing possible side effects of drugs***

| Drugs | Common side effects |
|---|---|
| Donepezil | nausea, muscle cramps, unusual tiredness or weakness loss of appetite, diarrhea, vomiting |
| Galantamine | weight loss, loss of appetite, dizziness, diarrhea, vomiting, nausea |
| Memantine | abnormal laboratory test results,balanceproblems,breathingdifficulties,constipation,feelingdizzy,headaches,hypersensitivityreactions,raised blood pressure. Sleepiness. |
| Rivastigmine | weight loss, vomiting, nausea, loss of strength, loss of appetite, indigestion, diarrhea. |
| Tacrine | Clumsiness or unsteadiness, Diarrhea,loss of appetite,nausea,vomiting |
| Bapineuzumab | Vasogenicoedema |
| Bryostatin 1 | nausea, fatigue, headache, vomiting, anorexia, anaemia, lymphopenia. |
| LY450139 Semagacestat | decrement of lymphocytes in spleen and thymus, hence change in immune system can be observed |
| PBT-2 | Headache, dizziness, somnolence |
| AVP923 | Behavioral problems |

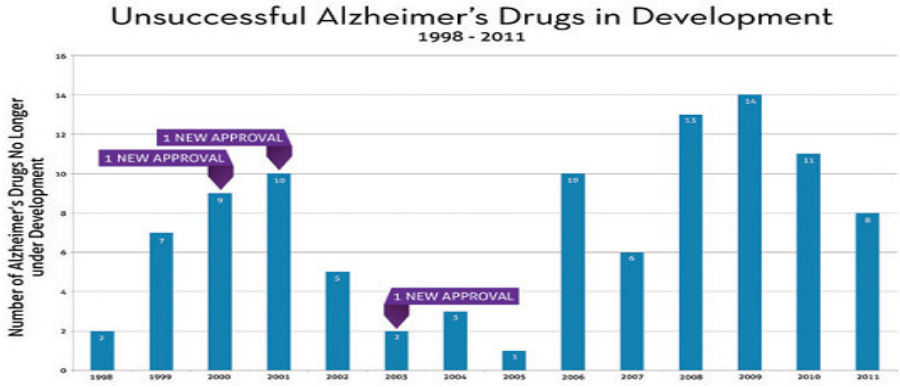


**Figure VIII**

***Ineffective attempts, since 1998, to develop more adequate drugs which will combat with this disease[58].***

***An ongoing research has been carrying out by biopharmaceutical research to find new treatment which have potential to treat or slowdown or prevent AD. Nonetheless, the highway from primitive investigation to new drug treatments is intensive with numerous setbacks. As number of scrutinization regarding AD has failed to gasp patients every year shown in figure VIII. For every failure we have to subsidize new path. (50, 57).***

## PLANT SECONDARY METABOLITES AND ALZHEIMER'S DISEASE: CURRENT SCENARIO

In plant physiology, secondary metabolites playa very important role like, pigmentation, resistivity to pathogens, growth astringency and bitterness of plant. Several plants have free radical scavenging property, which are present in the form carotenoids and flavonoids. Regular consumption of these nutritive substances may have beneficial effects. Many reports also support that, the plants having antioxidant property, helps in prevention from nocuous effect of oxidative stress on signal transduction and nerve growth factors in rats. They also reduce the effect of malfunctioning motor behavior in nerves. All these experiments, shows beneficial effect or capability of plants to cure neuronal disease but these are not directly related to AD[58]. Amongst all secondary metabolites, heterogenic group of benzo-ç-pyron derivative, which is known as flavonoids abundantly found in food products and beverages, mainly from fruits and vegetables[59] shown in table 5. There are other metabolites like, vitamin E (tocopherol), vitamin C (ascorbic acid), vitamin D (calciferol), isoflavonoid type, phytoestrogens, fatty acids, influences membrane function in many ways. Even in cancer, these metabolites attune the activity of membrane enzymes and receptors. The various protective affects due to dietary components has also taken as consideration because it can implicated on DNA damage in neurodegeneration, malignant growth to cancer[60].

## FLAVONOIDS

Flavonoids consist of two aromatic rings which are bound together by three carbon atoms that form an oxygenated heterocycle[61], divided into 6 classes: flavonols, flavones, anthocyanins and isoflavones. Catechins, quercetin and myricetin etc., are most common flavonoids[6]. Reveratrol, shows beneficial effect when it is consumed in equitable amount of red wine, it scavenges O2- and OH- invitro and lipid hydroperoxyl free radicals in case of dementia. Against neuroprotection the fruits and vegetables are invaluable, by influencing and modulating several cellular processes such as signaling, proliferation, apoptosis, redox balance and differentiation. The ability of these flavonoids to block TNF-α-induced CAM (cell adhesion molecules) expression could be due to their antioxidant properties63-65. Glutamate decreases the intracellular level of GSH by inhibiting the uptake of cystein which is necessary for GSH production, in addition quercetin and fisetin increase GSH levels in HT-22 cells[66-67].*Alcea pallida* shows promising results on free radical scavenging activity, which can be used for neurodegenerative disorders[68] .

## SAPONINS

Saponins mainly contains sugar moiety which consists of galactose, glucose, glucoronic acid, xylose, rhamnosepr methylpentose, which is glycisidically linked to hydrophobic aglycone (sapogenin) which may be triterpenoid and steroid in nature. Activaion of mGluR8 in pilocarpine instigated epileptic rats has been reported to have anticonvulsant[69-72] mGluR8 gene expression play an important role in the pathophysiology of pilocarpine induced temporal lobe epilepsy in rats and B. monneri extracts shows a regulatory effect on mGluR8 gene expression in epilepsy[73-74]. *Anemarrhenaasphodeloides* mitigate learning deficits caused by brain damage and aging in rodent[75-77]. Components isolated from AA are sarsasapogenin and timosaponin BII enhanced learning and memory in amyloid β peptide (25-35) - or scopolamine induced dementia in rats[77]. Some species of Thymus contains both terpenes and polyphenols possess antioxidant properties with free radical scavenging activity, inhibiting lipid peroxidation and also exhibited anti-AchE activity[78].

## ALKALOID

Rutaecarpine (Ru) is one of the alkaloid (quinazolinocarboline) isolated from *Evodiarutaecarpas*. It possesses a wide spectrum of pharmacological activities, like vasodilatation, anti-inflammation, antithrombosis[79-80]. In some literatures, it has been found that, the modification in the general structure of AChE and AChE inhibitors by including two components separated by a spacer group with compatible length, with aromatic ring binding with the PAS of AChE and with side chain terminal amino group interacting with catalytic site of AChE. By doing all these modification, rutaecarpine could improve AChE inhibitory activity based on docking studies[81]. Black Tea (*Camellia sinensis*) manifest about 78% of world population consumed tea and acquire neuroprotective properties under conditions like Parkinson's disease, ischemia and hypoxia.It was also found that harmine seeds of *Peganumharmala* is sequentially penetrating blood brain barrier inhibiting some early response genes.

**Table 4**
***Showing action of different secondary metabolites and their action on AD***

| Plant | Secondary metabolites | Protective action | References |
|---|---|---|---|
| Citrus fruits | Vitamins C | Modulation of the activity of membrane enzyme[60] | (60) |
| *Gingko biloba* | EGb 761 | Improve cognitive functions, protect against toxicity induced by Aβ- derived peptides on hippocampal cells[82] | (82) |
| Tea | Epicatechin | Against neuronal cell death due to oxidative stress[83] | (83) |
| Tea | Catechin polyphenols | Scavenging of radicals, activation of survival genes, iron chelating, cell signaling. Mitochondrion functioning[21] | (21) |
| Turmeric | Curcumin | Antioxidant properties, inhibit certain signal | (21) |

| | | | |
|---|---|---|---|
| | | transduction pathways[21] | |
| *Gingko biloba* | EGb 761 | Inhibition of Aβ oligomerization[82] | (82) |
| *Bacopamonneri* | Polyphenols | Antioxidant, anti inflammatory[21] | (21) |
| Green Tea | Catechin& 30-o-methyl-Epicatechin | Against oxidative damage, activation/ phosphorylation of signaling proteins for pro-survival pathways[83]. | (83) |
| Saffron | Saffron extract | Antioxidant anti-amyloidgenic activity[13] | (13) |
| Walnut | Walnut extract | Reducing generation of free radicals, inhibiting membrane damage and DNA damage[6] | (6) |
| Blueberry, cocoa | Blueberry, cocoa extract | Interactions with ERK signaling pathway, Antioxidant, anti-inflammatory[85] | (85) |
| Coffee | Di- caffeoylquinic acid | Acetyl cholinesterase inhibitory activity[21] | (21) |
| *Dispacusasper wall.* | Akebiasaponin D | Protects P12 cells[86] | (86) |
| *Isodonjaponicas* | CBNUO6 | Inhibition of NF-κB signaling pathway[87] | (87) |
| *Fritillariaebeiensis* | Labdanediterpenes | Against $MPP^+$induced neuronal cell death | (83) |
| Pepper | Piperine | Decrease peroxidation and acetylcholinesterase[88] | (88) |
| *Tripterygiumwilfordii* | Celastrol | Suppression of NF-κB pathway[42] | (42) |
| *Aspergillusterrus* | Isoterreulactone | Inhibit Acetylcholinesterase[28] | (28) |
| Vitamin E rich food | Vitamin E | Prevents lipid peroxidation[43] | (43) |
| *Trifolium pretense* L. *Spantholobussuberectus*, *Astragalusmongholicus Bunge* | Formononetin | Inhibit neuronl damage from NMDA exocitoxicity | (88) |
| Ceylon cinnamon | Cinnamonumzeylanicum | Anti tau[89] | (89) |
| Mulberry | Hygroxylstilbene | Pretreatment of SH-SY5Y cells[90] | (90) |
| Strawberry | Antioxidant polyphenols | PC12 cells[21] | (21) |
| Pomegranate | Phenolic antioxidant ellagic acid | SH-SY5Y cells[21] | (21) |
| Grape seed | Phenolic antioxidants and pro-anthocyanidins, Resveratrol | NF-κB,inflammation and oxidative stress[21] | (21) |
| Pappaya | β- carotene | bax/bcl-2 sensitive pathway, SH-SY5Y cells[90]. | (90) |
| Apple | S-adenosylmethionine | AChE level, expression of presenilin-1[90] | (90) |
| Green Tea | Epigallocatechingallate (EGCG) | Activity of protein kinase C, proteolytic processing of amyloid precursor protein, lipid peroxidation, Bax gene, NF-κB levels[90] | (90) |
| Coffee | Caffeine | c-FOS, transcription activating factors, presenilin-1, b secretase[90]. | (90) |
| *CatharanthusRoseus* | Caffeoylquinic acid | AChE[90] | (90) |
| Walnut | Ellagic acid | PC12 cell lines[21] | (21) |
| Saffron | Crocin | PC12 cells[21] | (21) |
| *Curcuma longa* | Curcumin | Heat shock proteins[21] | (21) |
| Pepper | Piperine | lipid peroxidation and AChE activity[21] | (21) |
| Cinnamon | Cinnamaldehyde, eugenol, cinnamyl acetate, and cinnamyl alcohol | cross the blood brain barrier (need to explore)[21] | (21) |
| Ginger | Bisabolene, zingiberene, and monoterpenes | AChE inhibitory activity, lipid peroxidation[21] | (21) |
| *Ginkgobiloba* | EGb761 | ROS level, SH-SY5Y Cells[21] | (21) |
| *Poncirus Trifoliate* | Methoxsalen | AChE inhibition[21] | (21) |
| *Salvia Officinalis* | | AChE inhibition[21] | (21) |
| *ScrophulariaBuergeriana* | KD501 | AChE inhibition[21] | (21) |
| *Salvia Officinalis* | | AChE inhibition[21] | (21) |
| *HuperziaSerrata* | Huperzine A | AChE inhibition, Bax and p53 genes, PC12 cells[21] | (21) |
| *BacopaMonnieri* | Brehmine, herpestine, nicotineandsaponin | AChE inhibition[21] | (21) |
| *PaeoniaSuffruticosa* | 1,2,3,4,6-penta-O-galloyl-b-D-glucopyranose | SH-SY5Y Cells[21] | (21) |
| *UncariaRhynchophylla* | Oxindole and indole alkaloids | Ab fibrillation[21] | (21) |
| *RosmarinusOfficinalis* | Carnosol and carnosic acid | Keap1/Nrf2 pathway[21] | (21) |
| *Galanthusworonowii* | Galanthamine | AChE inhibition[21] | (21) |
| *Magnolia Officinalis* | 4-O-methylhonokiol | AChE inhibition[21] | (21) |
| *CoriandrumSativum* | Flavonoid glycosides, caffenic acid | AChE inhibition[21] | (21) |

## CONCLUSION AND FUTURE PROSPECTS

Till date, many hypotheses were proposed to analyze the main causative agent for AD. In 1992 amyloid β cascade hypothesis was first proposed, assuming that β amyloid would be the suspect initiating pathogenesis of dementia. Hence, a series of exploration has been done and intensively focused on physiological and pathological processes. The enzymes responsible for cleavage of the presumably pathogenic amyloid beta from its precursor are: γ-secretase and BACE-1. Similarly, all of these many more causative agents have been found like oxidative stress, mutation in the gene coding amyloid peptide protein For all these causes many synthetic drugs are available in market like dopenezil, memantine, tacrine but the major setbacks of all were their side effects. In the junction of drug development using different models man drugs are in the track of validation. Due to this many drugs related to plant secondary metabolites come into interest to many researchers like, *Gingko biloba*, vitamin E, curcumin which are already commercialized. Regular consumption of these nutritive substances may prevent the effects of oxidative effect of cells which causes AD. So, for future, it really required it really required to get into department of disease proceedings and understand modification of AD, for this procedure, we need to know some specific answers of question like:

A) Which type of patients to be treated?
B) About the medication, which type for it is used for? How long will be these trials or medication goes?
C) Duration of medications and its trials?

Last but not the least, biological measures prove to be better tool to understand the outcomes of the trials, especially in clinical trials, to understand and measure the efficacy of drug.

## CONFLICT OF INTEREST

Conflict of interest declared none.

## REFERENCES


1. Nilsberth C, Danielsson WA, Eckman CB, Condron MM, Axelman K, Forsell C, Stenh C, Luthman J, Teplow DB, Yonkin SG, Naslund J, Lannfelt L, 2001. The “Arctic” APP mutation (E693G) causes Alzheimer’s disease by enhanced amyloid beta protofibril formation. Nature Neurosci. 2001; 4: 887-93.
2. Silvia M, Youdim HB. Assessing creativity with divergent thinking tasks.Exploring the reliability and validity of new subjective scoring methods. Free Rad Biol Med. 2004; 37: 304-17.
3. Essa MM, Vijayan RK, Gonzalez GC, MemonMA, Braidy N, Guillemin GG. Neuroprotective effect of natural products against Alzheimer’s disease. Neurochem Res. 2012; 37: 1829-42.
4. Christen Y. Oxidative stress and Alzheimer disease. Am J Clinic Nutr. 2000; 71: 621-29.
5. Wiseman HJ. Dietary influences on membrane function: importance in protection against oxidative damage and disease. J Nutr Biochem. 1996; 7: 2-15.
6. Rafii MS and Aisen PS. Intra and postoperative cetumaxomab in patients with epithelial ovarian cancer: safety and two year efficacy results from a multicentre, single arm, phase II study. BioMed Cent Med. 2009; 7:7-11.
7. Tian Z, Liu SB, Wang YC, Li X qiang, Zheng, L he, Zhao M. Neurexin regulates visual function via mediating transport to promote Rhodopsin maturation. Physiotherap Res. 2013; 10: 25-30.
8. Nowak L, Bregestovski P, Gubareff TD. Magnesium gates glutamate- activated channels in mouse central neurons. Brain. 1984; 176: 91-100.
9. Hardy J and Selkoe DJ. The amyloid hypothesis of Alzheimer’s disease: progress and problems on the road to therapeutics. Science. 2002; 297: 353-56.
10. Akhondzadeh S, Shafiee MH, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, Hejazi SS, Yousefi MH, Alimardani R, Jamshidi AH, Zare F, Moradi A.Saffron in the treatment of patients with mild to moderate Alzheimer’s disease: a 16-week, randomized and placebo controlled trial. Int J Clin Pharmacol Therap. 2009; 35: 1365-70.
11. Bruen PD, McGeown WJ, Shanks MF, Venneri A. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer’s disease. Brain. 2008; 131: 2455-63.
12. Spencer JEP. Flavonoids and brain health: multiple effects underpinned by common mechanism. Genes Nutr. 2009; 4: 243-50.
13. Wake G, Court J, Pickering A, Lewis R, Wilkins R, Perry E. CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. J Ethanopharmacol. 2000;69: 105-14.
14. Wischik CM, Novak M, Thogersen CH, Edwards PC, Runswick MJ, Jakes R, Walker JE, Milstein C, Roth M. Isolation of a fragment of tau derived from the core of the paired helical filament if Alzheimer disease. Proceed Nat Acad Sci USA. 1988; 85: 4506-10.
15. Vassar R, Benett BD, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amranta P, Leoloff R, Luo Y, Yi P, Fisher S, Fuller J, Edenson S, Lile J, Jarosinki MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treanor J, Rogers G, Citron M. Beta-secretase cleavage of Alzheimer’s amyloid precursor protein by the transmembrane aspartic protease BACE. Science. 1999; 286: 735-41.
16. Nunomura A, Perry G, Aliev G, Hirai K, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chaiba S, Atwood CS, Paterson RB, Smith MA, 2001. Oxidative damage is the earliest event in

Alzheimer disease J Neuropath Experiment Neuro. 2001; 60: 759-67.
17. Thal DR. Biomarkers in Alzheimer's disease. Brain Pathol. 2002; 12: 405-11.
18. GoateA, van Swieten J, Mann D, Lynch T, Heutink P. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. 1988; 393: 702-05.
19. Sethi G, AhnKS, Pandey MK, Aggarwal BB. Bilateral enlargement: an usual cause of massive cardiomegaly. Blood J. 2013; 109: 2727-327.
20. Gundke- Iqbal I, Nukina N, Quinlan M, Tung, YC Zaidi MS, Wisniewski HM. Abnormal phosphorylation of the microtubule-associated protein tau in Alzheimer's cytoskeletal pathology. J Biochem. 1986; 261: 6084-89.
21. Zhiyong L, Xinyi T, Chongwei Z, Yanhua L, Dongzhi W. Protective effects of hyperoside (quercetin-3-o-galactoside) to PC12 cells against cytotoxicity induced by hydrogen peroxide and tert-butyl hydroperoxide. Biochem Biomed Pharmacotherap. 2005; 59: 281-90.
22. Weggen S and Beher D. Molecular cosequences of amyloid precursor protein and presenillin mutations causing autosomal- dominant Alzheimer's disease. Alz Res Therap. 2012;4:9-14.
23. Areias FM, Rego AC, Oliveira CR, Seabra RM, 2001. Antioxidant effect of flavonoids after ascorbate/ Fe<sup> 2$^{+}$</sup>- induced oxidative stress in cultured retinal cells. Biochem Pharmaco.2001; 62:111-18.
24. Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Tau pathology in two dutch families with mutations in the microtubule-binding region of tau. Proceed Nat Acad Sci. 1986; 83: 4913-17.
25. Mohsen MMAE, Kuhnle G, Rechner AR, Schroeter H, Rose S, Jenner P, Rice-Evans CA. Uptake and metabolism of epicatechin and its access to the brain after oral ingestion. Free Rad Biol Med. 2002; 33: 1693-702.
26. Iqbal IG, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI.Lewy bodies contain epitopes both shared and distinct from neurofibrillary tangles. Proceed Nat Acad Sci. 2004; 34: 45-53.
27. Wolfee MS, Xia W, Ostazaewski BL, Diehl TS, Kimberly WT, Selkoe DJ. Two transmembraneaspartases in presenillin-1 required endoproteolysis and gamma- secretase activity. Nature. 1999; 398:513-17.
28. Selkoe DJ. Alzheimer's Disease: Genes, proteins and therapy. Physiol Rev. 2001; 81: 742-60.
29. Gong CX. Post translational modification of tau protein in Alzheimer's disease. J Neu Trans. 2005; 1739:198-10.
30. Cancino GI, Miller FD, Kalpan DR.p53haploinsufficiency causes tau hyperphosphorylation and tau kinase dysregulation in mouse models of aging and Alzheimer's disease. Neurobiol Aging. 2013; 34: 387-99.
31. Bell D, Berislav E, Zlokovic V. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol. 2009; 118:103-13.
32. Betram L, McQueen BM, Mullin K, Blacker D, Tanzi ER. Systematic meta- analyses of Alzheimer's disease genetic association studies: the AlzGene database. Nature Gen. 2007; 39:17-33.
33. Becker RE and Greig NH. Alzheimer's disease drug development in 2008 and beyond: Problems and opportunities. Curr Alz Res. 2008; 5: 356-57.
34. Williams RJ and Spencer JEP. Flavonoids, cognition, and dementia: actions, mechanism and potential therapeutic utility, for Alzheimer's disease. Free Rad Biol Med. 2012;52: 35-45.
35. Carvalho C, Cardoso S, Correia SC, Santos RX, Baldeiras I, Oliveira CR, Moreira PI. Dysfunction pro-ceramide, ER stress, and insulin/IGF signaling networks with progression Alzheimer's disease. Diabetes. 2012; 61: 1324-342.
36. Lin X, Koelsh G, Wu S, Downs D, Dashti A, Tang J. Requirement of NAD and SIR2 for life span extension by calorie restriction in *Saccharomyces cerevisae*. Proceed Nat Acad Sci. 2000; 97: 1456-60.
37. Brookmeyer R, Johnson E. Graham-Ziegler K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alz Demen. 2007; 3: 186-91.
38. Breteler MMB. Mapping out Biomarkers for Alzheimer's Disease. J Am Med Assoc. 2011; 305: 304-05.
39. Braak H and Braak E.Staging of Alzheimer-related cortical destruction. Int Pschogeriatr. 1998; 9: 257-61.
40. Ihara Y, Nukina N, Miura R, Ogawara M. The ubiquitin-proteosome system and the autophagic-lysosomal system in Alzheimer disease. J Biochem (Tokyo). 1986; 99:1807-10.
41. Butterfield DA, Launderback CM.The glutamatergic system and Alzheimer's disease therapeutic implication. Free Rad Biol Med. 2002; 32:1050-60.
42. Shin Kim H, Lim JY, Sui D, Hwang BY, Won TJ, Hwang KW, Park SY. Mutations of tumour necrosis factor-related apoptosis inducing ligand receptor-1 (TRAIL-R1) and receptor 2 (TRAIL-R2) genes in metastatic breast cancer. Antiviral Pub. 2009; 622:25-31.
43. Morris MC, Evans DA, Tangney CC, Beinias JL, Wilson RS, Aggarwal NT, Scherr A. Cerebral amyloid deposition and diffuse plaques in normal aging. Evidence for presymptomatic and very mild Alzheimer's disease. Am J Clin Nutr. 2005; 81: 504-14.
44. Muthaiya B, Essa MM, Chauhan V, Chauhan A, 2011. Protective effects of walnut extract against amyloid beta peptide-induced cell death and oxidative stress in PC12 cells. Neurochem Res. 2011; 36:2096-103.
45. Masliah E, Sisk A, Mallory M, Mucke L, Schenk D, Games D. Comparison of neurodegenerative pathology in transgenic mice over progression of Alzheimer's disease. J Neurosci. 1996; 16: 5795-11.
46. Sinha S, Andreson JP, Barbour R, Basi GS, Caccavello R, Davis D, Doan M, Harry DF, Frigon N, Hong J, Croak KJ, Jewett N, Keim P,

Knops J, Leiderburg I, Power M, Tan H, Tatsuno G, Tung J, Schenk D, Schenk D, Suomensaari SM, Wang S, Walker D, Zhao J, McConlogue L, John V. Purification and cloning of amyloid precursor protein-secretase from human brain. Nature. 1999;402: 537-40.

47. Nie BM, Jiang XY, Cai JX, Fu SL, Yang, LM, Hang Q, Lu PL, Lu Y. Regulation of lymphocyte development type specific interception of Notch signals. Neuropharmacol Elsevier. 2008; 54: 845-53.
48. Faith HM, Walter BJ, Qin X, Tesseur I, Kekonius L, Masliah TE, Paul HC, Kimberly LS, Karl WH, Lennart M, Robert MW, Yadong H. Carboxyl-terminal-truncated apoliporotein E4 causes Alzheimer's disease- like neurodegeneration and behavioral deficits in transgenic mice. Proceed Nat Acad Sci. 2003;100: 10966-71
49. Houlden H. Variant Alzheimer's disease with spastic paraparesis and cotton wool plaques is caused by PS-1 mutation that lead to exceptionally high amyloid-β concentrations. Ann Neurol. 2000; 48: 806-11.
50. Anonymys. Researching Alzheimer's Medicines: Setbacks and stepping stones "Factsheet". Alz Asso. 2013. Available from: (www.acimmune.com).
51. Hussain I, Powell D, Howlett DR, Tew DG, Meek TD, Chapman C, Gloger IS, Murphy K.E, Southan CD, Ryan DM, Smith TS, Simmons DL, Walsh FS, Colin D, Christen G. Identification of a novel aspartic protease (Asp 2) asb-screatase. Mol Cell Neurosci. 1999; 14:419-27.
52. Watkins JC and Evans RH.Excitatory amino acid transmitters. Ann Rev Pharmacol Toxico. 1981; 21:165-204.
53. KarranE, Mercken M, Stopper De S. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Mac Publ. 2011; 10:698-712.
54. Wurtman RJ. Amyloid beta induced pathological behaviours are suppressed by Ginkobiloba extract EGb 761 and Ginkgolides in transgenic *Caenorhabditiselegans*. Trend Neurosci. 1992; 15:117-21.
55. Yan R, Bienkowski MJ, Shuck M.E, Maio H, Tory MC, Pauley AM, Brashler JR, Stratman NC, Matthews NC, Buhl AE, Carter BD, Tomasselli AG, Parodi LA, Heiweikson RL, Gurney ME. System-based proteomic analysis of the interferon response human liver cells. Nature. 1999; 402: 533-37.
56. Selkoe DJ, Hardy S. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. J Sci. 2002; 297: 353-56.
57. Stokin GB, Lillo C, Falzone TL, Brusch RG, Rockenstein E, Mount SL.Axonnopathy and transport deficits early in the pathogenesis of Alzheimer's disease. Science. 2005; 307: 1282-88.
58. Xu J, Liu C, Guo P, Guo Y, Jin D, Song X, Sun Z, Gui L, Ma Y. Neuroprotectivelabdanediterpenes from *Fritillaria ebeiensis*. Frit, Elsevier 2011; 82: 772-76.
59. Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, Andreadis A, Wiederholt WC, Raskind M, Schellenberg GD. Tau is a candidate gene for chromosome 17 frontotemporal dementia. J Biochem(Tokyo). 1986; 99:1807-10.
60. Yu X, Wang L, Ma L, You R, Cui R, Ji D, Wu Y, C-f Yang Z-lin, Ji H. Alternate aggregation pathways of the Alzheimer @b-Amyloid Ppeptide: A@b association kinetics at endosomal pH. Pharmacol Biochem Behav. 2012; 101: 459-86.
61. Spencer JP, Abd El Mohsen MM, Minihane AM, Mathers JC. Biomarkers of the intake of dietary polyphenols: strengths, limitation and applications in nutrition research. Brit J Nutr. 2008; 99:12-22.
62. de Groot H, Raven U. Tissue injury by reactive oxygen species and the protective effects of flavonoids. Fundamen Clin Pharmacol. 1998; 12:249-55.
63. Marui N, Offerman MK, Swerlick R, Kunsch C, Rosen CA, Ahmad M, Alexander RW, Medford RM. Vascular cell adhesion molecule-1 (VCAM-1) gene transcription and expression are regulated through an antioxidant-sensitive mechanism in human vascular endothelial cells. J Clin Invest. 1993; 92:1866-74.
64. Kokura S, Rhoads MCA, Wolf RE, Yoshikawa T, Granger DN, Aw T. NF kappa B signaling in posthypoxic endothelial cells: relevance to E-selectin expression and neutrophil adhesion. J Vas Res. 2001; 38:47-58.
65. Choi JS, Choi YJ, Park SH, Kang JS, Kang YH. Flavones mitigate tumor necrosis factor-α-induced adhesion molecule upregulation in cultured human endothelial cells: Role of nuclear factor-kB[1]. J Nutr. 2004; 134:1013-19.
66. Murphy TH, Miyamoto M, Sastre A, Schnaar RL, Coyle JT. Glutamate toxicity in a neuronal cell line involves inhibition of cystein transport leading to oxidative stress. Neuron. 1089; 2:1547-58.
67. Ishige K, Schubert D, Sagara Y. Flavonoids protect neuronal cells from oxidative stress by three distinct mechanism. Free Rad Biol Med. 2001; 30:433-46.
68. Ertas A, Boga M, Gaziglu I, Yasil Y, Hasimi N, Ozaslam C, Yilmnz H, Kaplan M. Fatty Acid, Essential Oil and Phenolic Compositions of *Alcea pallida* and *Alceaaptero carpa* with Antioxidant, Anticholinesterase and Antimicrobial Activities. Chi Mai J Sci. 2016; 43:1143-53.
69. Jiang FL, Tang YC, Chia CC, Jay TM, Tang FR. Anticonvulsive effect of a selective mGluR8 agonist (S)-3,4-Dicarboxyphenylglycine (S-3,4-DCPG) in the mouse pilocarpine model of status epilepticus. Epilepsia. 2007; 48:783-92.
70. Attwell PJE, Kent NS, Jane DE, Croucher MJ, Bradford HF. Anticonvulsant and glutamate release-inhibiting properties of the highly potent metabotropic glutamate receptor agonist (2S, 2R, 3R)-2-(2,3-di-carboxycyclopropyl) glycone (DCG-IV). Brain Res. 1998; 805:138-43.
71. Gasparini F, Bruno V, Battaglia G, Lukic S, Leonhardt T, Inderbitzin W, Laurie D, Sommer B, Varney MA, Hess SD, Johnson EC, Khun R, Urwyer S, Sauer D, Portet C, Schmutz M, Nicoletti F, Flor PJ. (R, S)-4-phosphorno

phenylglycine, a potent and selective group III metabotropic glutamate receptor agonist, is anticonvulsive and neuroprotective in vivo. J Pharmacol Exp Therap. 1999; 289:1678-87.
72. Ruiz A, Walker MC, Fabian-Fine R, Dimitri MK. Endogenous zinc inhibits $GABA_A$ receptor in a hippocampal pathway. J Neurophysiol. 2004; 91; 1091-96.
73. Bhattacharya SK, Kumar A, Ghosal S. Antioxidant activity of *Bacopamonnieri* in rat frontal cortex, striatum and hippocampus. Phytotherap Res. 1999; 14:174-79.
74. Paulose CS, Chathu F, Khan SR, Krishnakumar A. Neuroprotective role of *Bacopa monnieri* in epilepsy and effect of glucose supplementation during Hypoxia: Glutamate receptor gene expression. Neurochem Res. 2008; 33: 1663-71.
75. Hu Y, Xia Z, Sun Q, Orsi A, Rees D. A new approach to the pharmacological regulation of memory, sarsapogenin improves by elevating the low muscraenic acetylcholine receptor density in brains of memory deficit in rat model. Brain Res. 2005; 1060:26-39.
76. Li TJ, Qui Y, Yang PY, Rui YC, Chen WS. Timasponin B-II improves memory and learning dysfunction induced by cerebral ischemia in rat. Neurosci Lett. 2007;421:147-51.
77. Quyang S, Sun LS, Guo SL, Liu X, Xu JP. Effects of Timosaponin on learning and memory abilities of rats with dementia induced by lateral cerebral ventricular injection of amyloid beta peptide. Di 1 junyi da xuexuebao. J Med Coll PLA. 2005; 25:121-26.
78. Kindl M, Blazekovic B, Bucar F, Vladimir-Knezevic S. Antioxidant and acetylcholinesterase potential of six thymus species. Hindawi. 2015; 403950:1-10
79. Tsai TH, Lee TF, Chen CF, Wang LCH. Thermoregulatory effects of alkaloids isolated from Wu-Chu-Yu in afebrile and febrile rats. Parmacol Biochem Behav. 1995; 50: 293-98.
80. Moon T, Murakami M, Kudo I, Kim HP, Son KH, Kang SS, Chang HW. A new class of COX-2 inhibitor, rutaecarpine from*Evodiarutaecarpa*. Immfla Res. 1999; 48: 621-25.
81. Wang B, Mai Y-Chi, Li Y, Hou JQ, Huang SL, Qu TM, Tan JH, Ann LK, Li Ding, Gu LQ, Huang ZS. Synthesis and evaluation of novel rutaecarpine derivatives as selective acetylcholinesterase inhibitors. Euro J Med Chem. 2010; 45:1415-23.
82. Lee VM, Balin BJ, Otvos L Jr, Trojanowski JQ. Characterization of a large deletion associated with a polymorphic block of repeated dinucleotides in the type III procollagen gene (COL3A1) a patient with Ehlers-Danlos syndrome type IV of Science. Am J Hum Gen. 1991;251: 675-78.
83. Rossi L, Mazzitelli S, Arciello M, Capo C.R, Rotilio G. Detection of plasma autoantibodies to brain tissue in young children with and without autism spectrum disorders. Neurochem Res. 2008; 33: 2390-400.
84. Yoo ID, Cho KM, Lee CK, Kim WG. Isoterreulactone A, a novel monoterpenoid with anti-acetylcholinesterase activity produced by *Aspergillus terreus*. Bioorg Med Chem Lett. 2005;15: 353-56
85. Packer L, Prilipko L, Christen Y, Heidelberg I. A comparative analysis of non offspring nursing. Germany: Spr-Ver. 1992; 12:36-49.
86. Heo HJ and Lee CY. Protective effects of quercetin and vitamin C against oxidative stress-induced neurodegeneration. J Agri Food Chem. 2009; 52:7514-17.
87. Zhang XD, Xiang LQ, Yang H, Wan WK. Chamical constituents and their acetyl cholinesterase inhibitory and antioxidant activities from leaves of *Acanthopanax henri*: potential complementary source against Alzheimer's disease. Arch Pharma Res. 2014; 37: 606-16.
88. Foster AC, Collins JF, Schwarcz R. A radio enzymatic assay for quinolinic acid. Neuropharmacol. 1983; 22:1331-42.
89. Ferreyra MLF, Rius SP, Casati P. Flavonoids: Biosynthesis, biological functions, and biotechnological application. Front Pla Sci. 2013; 3:1-15.